REMARKS

Applicants acknowledge the Examiner's statement that, in view of applicants' Statement Deleting Inventors under 37 C.F.R. § 1.63(d) filed June 29, 1999, the inventive entity of the instant application has been amended to delete David W. Thomas and Mihail N. Karpusus.

The specification has been reviewed for inadvertent typographical errors and identification of all trademarks.

Applicants state that the sequence of Gly116-Leu261 does not constitute the entirety of SEQ ID NO:1, rather Gly116-Leu261 is embedded within SEQ ID NO:1.

The Abstract

Applicants have amended the Abstract to more particularly describe the claimed invention. None of the amendments to the Abstract constitutes new matter.

The Drawings

Applicants acknowledge the Examiner's statement that the formal drawings filed in this application comply with 37 C.F.R. § 1.84.

The Claims

Applicants have cancelled claims 102, 109, 110, 111, 128 and 129, in order to more distinctly claim the present

invention and to expedite prosecution. This cancellation of claims should not be interpreted as applicants' acquiescence to any rejection in the outstanding Office Action. Applicants expressly reserve the right to pursue the subject matter of the cancelled claims in one or more applications claiming priority herefrom under 35 U.S.C. § 120.

Applicants have amended claims 1, 103, 104, 112, 117, 119 and 121 to 127 in order to more particularly claim the invention of the instant application. None of these amendments constitutes new matter. Specifically, support for the recitation of "Fab, F(ab')2 or single chain antibody", is provided in cancelled claim 111 and in the specification at page 13, lines 9-22. Applicants have also added claims 130-131, to recite subject matter formerly recited in claims 125 and 126, respectively.

As mentioned above, applicants have cancelled former claims 102, 109, 110, 111, 128 and 129 in order to: (1) more distinctly claim the invention of the instant application and (2) expedite prosecution. To some degree, the outstanding rejections are rendered moot by the claim cancellations and amendments herein. Applicants address below the Examiner's remaining contentions.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 128 and 129 stand rejected under 35 U.S.C. § 112, first paragraph, based on asserted lack of written

description and enablement. The Examiner contends that "there appears to be insufficient written description as well as guidance and direction in the specification as filed for ... coadministration of a compound of the invention along with a gene therapy vector or a therapeutic agent as a dependent claim of treating atherosclerosis (and accelerated atherosclerosis)." The Examiner also contends that "undue experimentation would be required of one skilled in the art to practice the claimed methods to 'gene therapy vectors', 'therapeutic agents', 'antigenic pharmaceuticals' and 'blood products'[.] commensurate in scope with the claimed invention using the teaching of the specification."

Applicants disagree. However, in order to accelerate allowance of this application, applicants have cancelled claims 128 and 129. This cancellation is without prejudice to applicants' right to file for and obtain claims directed tothe cancelled subject matter in applications claiming priority herefrom under 35 U.S.C. § 120. This cancellation of claims renders moot the rejection under 35 U.S.C. § 112, first paragraph.

Applicants acknowledge the Examiner's statement that the 5c8 antibody is enabled, based on the availability of the 5c8

antibody produced by the hybridoma designated as ATCC HB 10916, as evidenced by United States patent 5,474,771.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 128 and 129 stand rejected under 35 U.S.C. § 112, second paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant[s] regards as the invention essentially for the reasons set forth in the previous Office Actions (Paper Nos. 22/25)." More specifically, the Examiner asserts that there is insufficient guidance and direction in the specification as filed for providing for the concepts of gene therapy vectors, therapeutic agents, antigenic pharmaceuticals and blood products together with atherosclerosis (and accelerated atherosclerosis).

Applicants disagree with the Examiner's contentions. However, the cancellation of claims 128 and 129 renders moot the rejection under 35 U.S.C. § 112, second paragraph.

The Rejection Under 35 U.S.C. § 102(e)

Claims 1, 103-105, 109-117 and 128-129 stand rejected under 35 U.S.C. § 102(e) as being "anticipated by" Wilson al. (United States patent 5,652,224). More specifically, the Examiner asserts that Wilson et al. "teaches the use of gene

therapy vectors in combination with immunomodulators such as anti-CD40L antibodies . . . to treat various disorders including atherosclerosis . . ." Additionally, the Examiner contends that "the claimed methods recite 'comprising' which leaves the claim open for the inclusion of unspecified ingredients even in major amounts." Applicants traverse.

Wilson et al. is directed at the "treatment of metabolic disorders caused by the accumulation of LDL [low density lipoproteins] in plasma, such as familial hypercholesterolemia or familial combined hyperlipidemia." (Abstract). Wilson et al. discloses gene therapies said to be useful to treat and/or supplement current treatments for such lipoprotein metabolic disorders (column 7, lines 11-13). In essence, Wilson et al. teaches a gene therapy treatment which provides a genetically deficient patient with supplemental amounts of a human VLDL (very low density lipoprotein) receptor, in a location in the body where it is not normally present, i.e., in the liver.

To the contrary, applicants' claims are directed to the treatment of atherosclerosis in a subject using an antibody, a Fab, a F(ab')2 or a single chain antibody, which inhibits the interaction between CD40 ligand and CD40, thereby preventing the

activation of CD40-bearing cells, which play a role in atherosclerosis. Thus, applicants' methods are effective for treating atherosclerosis, irrespective of whether or not the patient suffers from an underlying metabolic disorder. Thus, the patient population targeted by the methods of Wilson et al. is different from that targeted by applicants' methods.

Furthermore, in the context of use of immune modulators, Wilson et al.'s focus is simply to inhibit neutralizing antibody formation (column 16, lines 36-40). More particularly, an immune modulator is defined in Wilson et al. as "an agent capable of inhibiting the formation of neutralizing antibodies directed against the recombinant vector of this invention or capable of inhibiting cytotoxic T lymphocytes (CTL)." Contrary to the Examiner's assertion, Wilson et al.'s "co-administration of immune modulators in order to inhibit immune responses" is clearly limited to the prevention of immune responses which develop as a result of delivery of Wilson et al.'s gene therapy vector.

For all of these reasons, nothing in Wilson et al. teaches or suggests applicants' methods for treating atherosclerosis in a subject comprising the step of administering to said subject an antibody, a Fab, a F(ab')2 or a single chain

antibody, which inhibits the interaction between CD40 ligand and CD40, thereby preventing the activation of CD40-bearing cells. Accordingly, the § 102(e) rejection should be withdrawn.

The Rejection Under 35 U.S.C. § 103

Claims 1 and 103-129 stand rejected under 35 U.S.C. § 103 as being "unpatentable over Wilson et al. (United States patent 5,652,224) in view of art know methods of generating modified antibodies of interest, as acknowledged by applicant on pages 13-15 of the instant application and in view of Lederman et al. (WO 93/09812). . ." The Examiner contends that "[o]ne of ordinary skill in the art at the time the invention was made would have been motivated to select the ability of CD40L-specific antibodies in combination with a gene therapy to inhibit atherosclerosis." Applicants traverse.

As detailed above, Wilson et al. is directed to gene therapy which provide a genetically deficient patient with supplemental amounts of a human VLDL (very low density lipoprotein) receptor, in a location in the body where it is not normally present, i.e., in the liver. Wilson et al.'s use of immune modulators is limited to the prevention of immune responses which develop as a result of delivery of Wilson et

al.'s gene therapy vector. Thus, even if combined with Lederman et al., or the art know methods of generating modified antibodies of interest cited on pages 13-15 of the instant application, Wilson et al. does not teach or suggest applicants' methods for treating atherosclerosis in a subject comprising the step of administering to said subject an antibody, a Fab, a F(ab')2 or a single chain antibody, which inhibits the interaction between CD40 ligand and CD40, thereby preventing the activation of CD40 bearing cells. Furthermore, neither White et al. nor Lederman et al. teaches or suggests the specific dosages and administration regimens of the antibody, Fab, F(ab')2 or single chain antibody, which inhibits the interaction between CD40 ligand and CD40, thereby preventing the activation of CD40 bearing cells, as recited in various claims of this application. In the absence of such teaching or disclosure, the Examiner's conclusion of obviousness represents no more than improper hindsight reasoning in view of applicants' disclosure. In re Ochiai makes clear the impermissibility of such hindsight-based obviousness analysis. In re Ochiai, 71 F.3d 1565, 1569-1570, 37 USPQ2d 1127, 1131-1132 (Fed. Cir. 1995).

Applicants request that the Examiner consider the foregoing amendments and remarks, and pass this application to issue.

Respectfully submitted,

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August 2, 2001

Lillian Garcia

Name of person signing

Lillian Garcia

Signature of person signing

APPENDIX A

IN THE ABSTRACT

Please amend the Abstract as follows:

Activation of cells bearing CD40 on their [cell] surface by CD40 ligand is inhibited by contacting the cells with an agent capable of inhibiting interaction between CD40 ligand and the cells[, in an amount effective to inhibit activation of the cells]. Activation of cells bearing CD40 on their surface by CD40 ligand in a subject is inhibited by administering to the subject an agent capable of inhibiting [the] interaction between CD40 ligand and the cells[, in an amount effective to inhibit activation of the cells]. Conditions dependent on CD40 ligand-induced activation of CD40-bearing cells are treated, in particular atherosclerosis.

IN THE CLAIMS

Please amend the claims as follows:

1. (Twice Amended) A method for treating atherosclerosis in a subject comprising the step of administering to said subject an antibody, [or portion thereof,] a Fab, a F(ab')2 or a single chain antibody, which binds specifically to a protein specifically bound by monoclonal antibody 5c8, produced by the hybridoma having ATCC Accession No. HB 10916.

103. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, inhibits binding of CD40 ligand to

CD40 on the surface of endothelial cells, fibroblasts, epithelial cells, T cells, basophils, macrophages, or dendritic cells in said subject.

104. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is effective to inhibit transmigration of inflammatory cells across the barrier of endothelial cells in said subject.

112. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is selected by a screening method, which comprises the steps of:

(a) isolating a sample of cells comprising endothelial cells, fibroblasts, epithelial cells, T cells, basophils, macrophages or dendritic cells;

(b) culturing said sample under conditions permitting activation of the CD40-bearing endothelial cells, fibroblasts, epithelial cells, T cells, basophils, macrophages or dendritic cells;

(c) contacting said sample with:

(i) cells expressing a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916, or

(ii) a protein which is specifically recognized by monoclonal antibody 5c8 produced by the hybridoma having ATCC Accession No. HB 10916,

under conditions which permit activation of said CD40-bearing endothelial cells, fibroblasts, epithelial cells, T cells, basophils, macrophages or dendritic cells;

(d) contacting said sample with an antibody, [or portion thereof,] a Fab, a F(ab')2 or a single chain antibody, under conditions which permit said antibody, Fab, F(ab')2 or single chain antibody, to inhibit activation of said CD40-bearing endothelial cells, fibroblasts, epithelial cells, T cells, basophils, macrophages or dendritic cells; and

(e) determining whether said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is capable of inhibiting activation of said CD40-bearing endothelial cells, fibroblasts, epithelial cells, T cells, basophils, macrophages or dendritic cells.

117. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject by a parenteral route.

119. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or

single chain antibody, is administered to said subject by sustained release administration.

121. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject at a dosage range of between about 0.01 and 200 mg/kg body weight of said subject.

122. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject at a dosage range of between about 0.01 and 50 mg/kg body weight of said subject.

123. (Amended) The method according to claim 1, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject at a dosage range of between about 1 and 30 mg/kg body weight of said subject.

124. (Amended) The method according to any one of claims 121 to 123, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject at intervals ranging from each day to every other month.

125. (Amended) The method according to any one of claims 121 to 123, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject daily for the first three days of treatment, after which the compound is administered to said subject every 3 weeks[, with each administration being intravenously at 5 or 10 mg/kg body weight of said subject].

126. (Amended) The method according to any one of claims 121 to 123, wherein said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject daily intravenously [at a dosage of 5 mg/kg body weight of said subject] for the first three days of treatment, after which the antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject subcutaneously or intramuscularly every week [at a dosage of 10 mg/kg of said subject].

127. (Amended) The method according to any one of claims 121 to 123, wherein a single dose of said antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, is administered to said subject parenterally at 20 mg/kg body weight of said subject, followed by administration of the antibody, [or portion thereof,] Fab, F(ab')2 or single chain antibody, subcutaneously or intramuscularly every week at a dosage of 10 mg/kg [per subject] body weight of said subject.

Please add the following claims:

130. (Added) The method according to claim 125, wherein said antibody, Fab, F(ab')2 or single chain antibody is administered to said subject by intravenous administration at a dosage of 5 or 10 mg/kg body weight of said subject.

131. (Added) The method according to claim 126, wherein said antibody, Fab, F(ab')2 or single chain antibody is administered to said subject daily intravenously at a dosage of 5 mg/kg body weight of said subject for the first three days of treatment, after which said antibody, Fab,

F(ab')2 or single chain antibody is administered to said subject subcutaneously or intramuscularly every week at a dosage of 10 mg/kg body weight of said subject.